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Review

Role of nuclear bodies in apoptosis signalling

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ABSTRACT

Promyelocytic leukemia nuclear bodies (PML NBs) are dynamic macromolecular multiprotein complexes that recruit and release a plethora of proteins. A considerable number of PML NB components play vital roles in apoptosis, senescence regulation and tumour suppression. The molecular basis by which PML NBs control these cellular responses is still just beginning to be understood. In addition to PML itself, numerous further tumour suppressors including transcriptional regulator p53, acetyl transferase CBP (CREB binding protein) and protein kinase HIPK2 (homeodomain interacting protein kinase 2) are recruited to PML NBs in response to genotoxic stress or oncogenic transformation and drive the senescence and apoptosis response by regulating p53 activity. Moreover, in response to death-receptor activation, PML NBs may act as nuclear depots that release apoptotic factors, such as the FLASH (FLICE-associated huge) protein, to amplify the death signal. PML NBs are also associated with other nuclear domains including Cajal bodies and nucleoli and share apoptotic regulators with these domains, implying crosstalk between NBs in apoptosis regulation. In conclusion, PML NBs appear to regulate cell death decisions through different, pathway-specific molecular mechanisms.

1. Introduction

Apoptosis is a vital process both in normal development and in the prevention of malignant cell growth. Apoptosis can occur via two principal routes, the intrinsic and the extrinsic pathway [1,2]. The extrinsic pathway is triggered by the binding of death ligands of the TNF (tumour necrosis factor) superfamily, for instance Fas ligand, TNFα or TRAIL (TNF-related apoptosis-inducing ligand), to their receptors on the cell surface, such as CD95/Fas or the TNF receptor. This results in the recruitment of the death inducing signalling complex (DISC) at their intracellular domains. The DISC promotes the cleavage and thereby activation of initiator caspases, most prominently caspase-8, leading to activation of effector caspases, such as caspases 3 and 9, and eventually to cell death. The extrinsic pathway is thought to be the body's own way of controlling malignant cell growth, as for instance TRAIL was shown to predominantly kill primary cancer cells or cancer cell lines as compared to normal tissue [3]. The intrinsic apoptosis pathway requires pro-apoptotic molecules of the Bcl-2 (B-cell lymphoma-2) family, which act primarily at mitochondria [4]. The activation of these proteins leads to the loss of the mitochondrial membrane potential, cytochrome *C* release and to the formation of the apoptosome. This apoptosome, which among other regulators contains Apaf-1 (apoptotic protease-activating factor 1) and caspase-9, can in turn activate a caspase cascade and trigger apoptosis [5]. This pathway is predominantly activated in response to irradiation or other cytotoxic stress and is therefore exploited in cancer therapy by ionizing radiation (IR) or chemotherapeutic drugs such as doxorubicin or etoposide. However, these chemotherapeutic drugs can also upregulate death receptors and their ligands and thus mediate apoptosis induction via the extrinsic pathway (recently reviewed in [6]). Extrinsic and intrinsic pathways converge in some cell species, so-called type II cells, in which activation of the DISC does not directly activate effector caspase-3 in the cytoplasm, but upon caspase-8 activation at the plasma membrane engages the mitochondrial pathway in an as yet not fully clarified mechanism, leading to apoptosome formation and cell death [2]. A master regulator of both intrinsic and extrinsic apoptotic pathways is the p53 protein, which acts as a sensor of DNA damage and cytotoxic stress and enhances the transcription of genes coding for many pro-apoptotic proteins such as the CD95 ligand, but also several caspases and Bcl-2 family members, sensitizing cells to various kinds of apoptotic stimuli (recently reviewed in [7,8]).

The nucleus of mammalian cells is a remarkably complex organelle, suborganized in multiple nuclear domains, including the heterogeneous family of macromolecular nuclear bodies (NBs), including Cajal bodies and PML NBs [9]. In this review we discuss the current knowledge about the role of PML NBs in apoptosis regulation, and disclose potential crosstalk with other types of NBs.

2. The PML nuclear body (PML NB)

Within the last decade, the doughnut-shaped subnuclear domains characterized by the promyelocytic leukemia protein (PML) have

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emerged as important regulators of cell cycle, defense against viral infection and prevention of transformation, DNA repair, regulation of transcription and, importantly, the induction of apoptosis and cellular senescence [10,11]. Intriguingly, it was shown that PML knockout mice are viable, but very susceptible to chemically induced carcinogenesis [12], and that overexpressed PML inhibits tumour formation in nude mice [13], suggesting that the PML protein may act as a tumour suppressor. This is at least in part due to the central role of PML in apoptosis induction, as PML knockout cells are largely protected against both p53-dependent and -independent apoptosis induction, e.g. induced by IR, interferons, ceramide, TNFα and CD95 activation, and also to oncogene-induced senescence [12,14].

PML NBs exist in almost all mammalian cells and their diameter ranges from about 200nm to 1μm in size. PML NBs are dynamic structures that move within the cell nucleus in intimate contact with the surrounding chromatin [15]. In addition to PML itself, they contain the Sp100 protein as a second constitutive component, and these two proteins appear to be highly modified with SUMO (small ubiquitin-related modifier) [16]. PML, the organizer of PML NBs, contains three covalent SUMO modification sites and one SUMO interaction motif (SIM), which non-covalently binds SUMO [17]. Most PML NB components are also sumoylated or bind to SUMO [16], indicating a fundamental role of SUMO in PML NB formation and recruitment of other proteins to PML NBs. Recent data obtained in yeast even suggest that PML may act as a SUMO E3 ligase [18]. It will be interesting to see whether this finding can be transferred to mammalian cells.

The PML protein contains an N-terminal *R*ING finger, which is characteristic for E3 ligases, two *B*-boxes and a leucine-rich *c*oiled-*c*oil domain, which are encoded by the first 3 exons of the *PML* gene, and thus belongs to the RBCC family. However, 7 groups of isoforms (PML-I to VII) have been described which differ in their C-termini, due to alternative splicing of exons 4 to 9 [19,20] (Fig. 1). When single isoforms are exogenously expressed in *PML−/−* cells, they form distinct structures in the nucleus that clearly differ from each other [21]. The different PML isoforms may therefore bind their own subset of interaction partners and thereby fulfil, in part, non-redundant functions in the cell, although isolated expression of single PML isoforms does not reflect the physiological situation in the cell where multiple isoforms appear to be expressed in combination and contribute to PML NB structure. Although the most abundant isoforms are PML-I and PML-II [21], the best investigated isoform is probably PML-IV, which regulates the recruitment and activation of p53 in PML NBs [22], facilitating apoptosis or cellular senescence upon cytotoxic stress. Moreover, PML-IV and also PML-III were shown to exhibit antiviral activity [23]. Recent kinetic analyses with several GFP-tagged PML isoforms point to PML-V as potential scaffold of the PML NBs, since it shows the longest residence time [143]. Further analysis, namely specific depletion of the endogenous PML proteins, will clearly help to clarify which of the known PML functions is mediated by which PML isoform(s).

Besides the “conventional” PML NB, a number of PML-containing nuclear structures have been described lately. For instance, in mitosis, PML-containing structures are formed that differ strongly from interphase bodies, since they do not contain Sp100, and were therefore termed mitotic accumulations of PML protein (MAPPs) [24,25]. A further type of PML-containing nuclear substructures is the ALT (alternative lengthening of telomeres)-associated NBs [26], which were found in telomerase-negative cancer cell lines that utilize a homologous recombination mechanism to maintain their telomere length and to circumvent replicative senescence [27]. In ALT cells, PML-containing bodies were found to colocalize with telomeric DNA, and ALT NBs may play a role in homologous recombination as well as acting as sensors for critically short telomeres. The ALT NBs have been shown to contain DNA repair proteins [28,29], checkpoint kinase ATM (ataxia-telangiectasia mutated) and p53, and both proteins can be activated in response to telomere shortening; however, the affected cells mostly respond with cell cycle arrest and cellular senescence rather than apoptosis.

PML NBs have been shown to contain a variety of enzymes and transcription factors. The nuclear protein database lists close to 80 proteins that localize to NBs (http://npd.hgu.mrc.ac.uk/compartments/pml.html), including DNA damage responsive proteins such as the DNA double-strand break (DSB) Mre11/Rad50/NBS1 (MRN) sensor complex [30–32], Bloom's syndrome helicase [33] and critical apoptosis regulators such as the transcriptional repressor Daxx [33,34], tumour suppressor p53 [14,22,35,36], CBP [14,22,37,38], HIPK2 [38,39], the

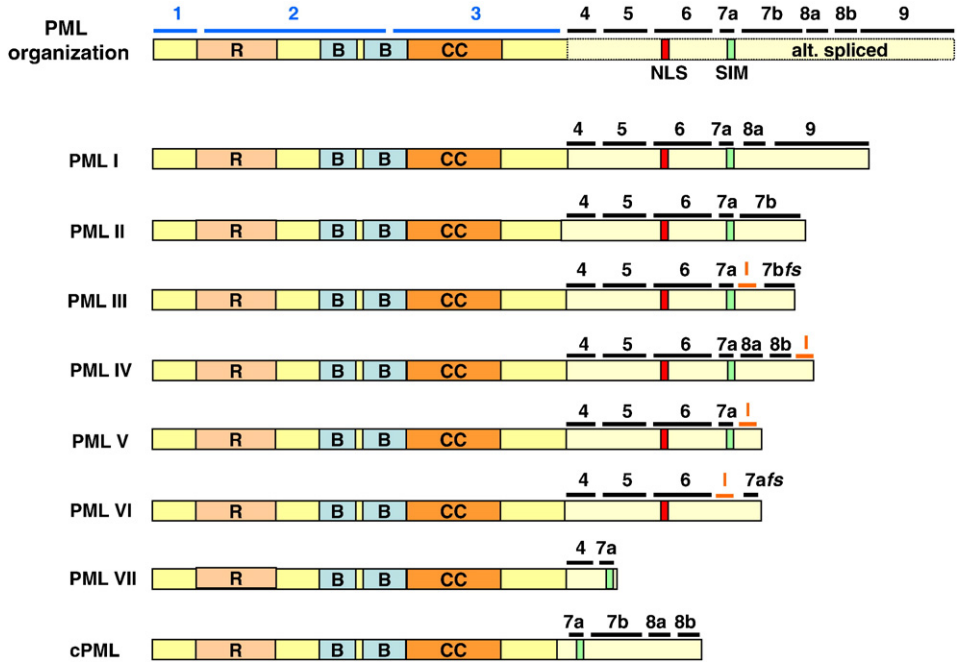

Fig. 1. PML isoforms. The first three exons, marked in blue, are present in every isoform. The seven subgroups are defined via alternative splicing of exons 7 to 9, but more recently, isoforms have been described which are alternatively spliced in the region between exons 4 and 6, sometimes resulting in cytoplasmic PML proteins.

Table 1
PML NB components associated with the DNA damage response and apoptosis regulation

Protein	Function	Associated disease	Refs.
ATM	S/T kinase, checkpoint signalling	Ataxia-telangiectasia	[29]
ATR	S/T kinase, checkpoint signalling	Seckel syndrome	[139]
BLM	RecQ family helicase	Bloom's syndrome	[33]
CBP	Acetyl transferase	Rubinstein–Taybi syndrome	[37]
Chk2	S/T kinase, checkpoint signalling		[97]
CK1	Ser/Thr kinase		[50]
CK2	Ser/Thr kinase		[140]
Daxx	Transcriptional corepressor, scaffold		[33,34]
Dlk/ZIPK	S/T kinase		[141]
FLASH	Scaffold; apoptosis/cell cycle regulation		[41]
HAUSP	Ubiquitin protease		[75–77]
HIPK2	S/T kinase		[38,39]
MDM2	E3 ubiquitin ligase		[42]
MRE11	MRN complex, DNA damage response	Ataxia-telangiectasia-like	[30]
NBS1	MRN complex, DNA damage response	Nijmegen breakage syndrome	[30]
p300	Acetyl transferase, E3 ubiquitin ligase?		[142]
p53	Transcription factor, apoptosis/cell cycle regulation	Li–Fraumeni syndrome	[14,22,35,36]
Par-4	aPKC inhibition		[93,95]
Piasy	SUMO E3 ligase		[103]
PML	Scaffold, transcriptional regulator	APL	[33]
pRb	Transcription factor, scaffold	Retinoblastoma	[40]
RNF4/ SNURF	Sumo-dependent E3 ubiquitin ligase		[137,138]
SirT1	Class III histone deacetylase		[71]
Sp100	Scaffold?		[16]
THAP1	DNA binding protein, transcription factor		[95]
TIP60	Acetyl transferase		[68]

retinoblastoma protein pRb [40], FLASH [41], and many components of the ubiquitin/SUMO protein modification systems, for instance the p53 ubiquitin ligase MDM2/HDM2 (mouse/human double minute 2) [42] and the ubiquitin ligase RNF4 (ring finger protein 4), which seems to degrade PML (see below). A list of the PML NB components linked to apoptosis regulation is shown in Table 1. Interestingly, most PML NB proteins are transient residents and are recruited or released upon different cellular stress signals. Most prominently, tumour suppressor p53 has been shown to associate with PML NBs after DNA damage induced by IR, UV or treatment with agents such as cisplatin or adriamycin. At the PML NB, p53 can be phosphorylated at serine residue 46 after lethal DNA damage (see below), and it can be acetylated by acetyl transferases such as Tip60 (Tat-interactive protein 60), CBP or p300, which enhances the activity of p53 towards its pro-apoptotic target genes. This will be discussed below in more detail.

3. PML NBs and p53 regulation

The *p53* gene is mutated in more than 50% of human cancer, and in the presence of an intact gene, the tumour suppressor p53 is often inactivated by other mechanisms, such as upregulation of its E3 ubiquitin ligases MDM2/HDM2, Pirh2 and COP1 [43]. In unstressed, healthy cells, p53 levels are kept low via proteasomal degradation [43]. In response to many kinds of stress, including UV and IR, hypoxia, DNA-damaging chemotherapeutic drugs or redox stress, p53 is stabilized and activated and can induce the transcription of its target genes, leading to cell cycle arrest, senescence or apoptosis [44]. Interestingly, PML itself was recently found to be a p53 target gene [45], suggesting a positive feedback loop for p53-dependent cell fate regulation. Upon DNA damage p53 is recruited into PML NBs where its apoptosis- and senescence-driving activity is regulated by its interaction with PML-IV and CBP, which control p53 Lys382 acetylation [14,22,35,36]. Depending on the strength of genotoxic stress, p53 is differentially modified and activates distinct sets of target genes. For instance, the *p21* gene is already activated after mild cell damage [46], and its expression blocks cell cycle progression to allow repair of the damage. Sublethal damage already leads to phosphorylation of p53 at serine residues 15 and 20 and at threonine 18, resulting in the dissociation of PML from MDM2/HDM2 (reviewed in [47]). Ser20 phosphorylation can be mediated by checkpoint kinase Chk2, which localizes to PML NBs and exits PML NBs upon DNA damage [48]. Casein Kinase 1 (CK1) can phosphorylate p53 on Ser9 and Thr18 [49], and this phosphorylation is enhanced by PML-IV [50]. In addition, CK1 directly phosphorylates MDM2 in the acidic loop, again weakening p53-MDM2-interaction (reviewed in [51]). The induction of pro-apoptotic p53 target genes, such as *Puma*, *p53AIP* and *Bax*, is strongly correlated with phosphorylation of Ser46 of p53 [52], which enhances p53 acetylation at Lysine 382 by CBP/p300 [38]. In parallel, Ser46 phosphorylation leads to isomerisation of p53 by the peptidyl prolyl-isomerase Pin1, resulting in the dissociation of p53 from its inhibitor iASPP (inhibitory apoptosis stimulating protein of p53) [53], and also from the ubiquitin ligase MDM2 [54]. Pin1 was also shown to increase the acetylation of p53, but some evidence suggests that although Pin1 was shown to partially reside in PML NBs [55,56], it may also act on promoter-associated p53 [53]. Conversely, phosphorylation-dependent degradation of unsumoylated PML was recently shown to be facilitated by Pin1 [55], which significantly inhibited apoptosis induction by hydrogen peroxide in a breast cancer cell line. This indicates that Pin1 exerts different functions in stressed and unstressed cells, underscoring its multifunctionality (reviewed in [57]).

Several kinases have been described to phosphorylate Ser46 on p53 in response to DNA damage: p38 [58], DYRK2 (dual-specificity tyrosine-phosphorylation regulated kinase 2) [59], Cdk5 (cyclin-dependent kinase 5) [60] and HIPK2 [38,39]. Of these, the function of HIPK2 has been most thoroughly investigated, and a close link to PML NBs has been identified. In unstressed cells HIPK2 levels are kept low by the ubiquitin ligases Siah-1 (seven in absentia homolog-1) [62] and WSB-1 [63] and it mainly resides in the nucleoplasm and in NBs which may correspond to polycomb bodies [61]. Upon cellular stress, degradation of HIPK2 is inhibited via ATM or the ATM- and Rad3-related kinase ATR [62] and a fraction of HIPK2 is recruited to PML NBs, where it colocalizes with p53 and presumably phosphorylates p53 on Ser46 [38,39]. In addition, HIPK2 binds the acetyl transferase CBP and enhances CBP-dependent p53 acetylation at Lys382 [38], which contributes to full activation of p53. HIPK2 can only efficiently phosphorylate p53 in the presence of PML [64], and also the PML NB component Sp100 seems to be important for this function [65], indicating that PML NBs could indeed be the site of Ser46 phosphorylation. HIPK2-mediated phosphorylation of p53 occurs after various kinds of DNA damage [38,39,66,67] and thus represents a central mediator in the apoptosis-regulating properties of PML NBs. Interestingly, earlier work revealed that oncogenic Ras-induced cellular senescence also involves CBP-mediated acetylation of p53 at Lys382 [14]. It is currently unclear whether HIPK2 is also involved in this process.

UV irradiation also induces the accumulation of TIP60 at PML NBs [68]. TIP60 belongs to the MYST family of acetyl transferases and is able to acetylate p53 at Lys120, and this acetylation was also shown to facilitate p53-dependent apoptosis [69,70]. An additional layer of complexity is added by the finding that the histone deacetylase SIRT1 can also localize to PML NBs and can reduce the acetylation of p53 at Lys382 and thereby counteract apoptosis induction upon DNA damage [71,72]. Intriguingly, the transcriptional repressor Daxx may also play a role in p53-dependent apoptosis associated with PML NBs [73]. A recent report showed an interaction of Daxx with the HIPK2 interactor and -activator axin [74], increasing the phosphorylation of p53 at Ser46. Moreover, under steady-state conditions, Daxx can form a ternary complex with MDM2 and the deubiquitinating enzyme HAUSP (herpesvirus associated ubiquitin-specific protease), enhancing MDM2

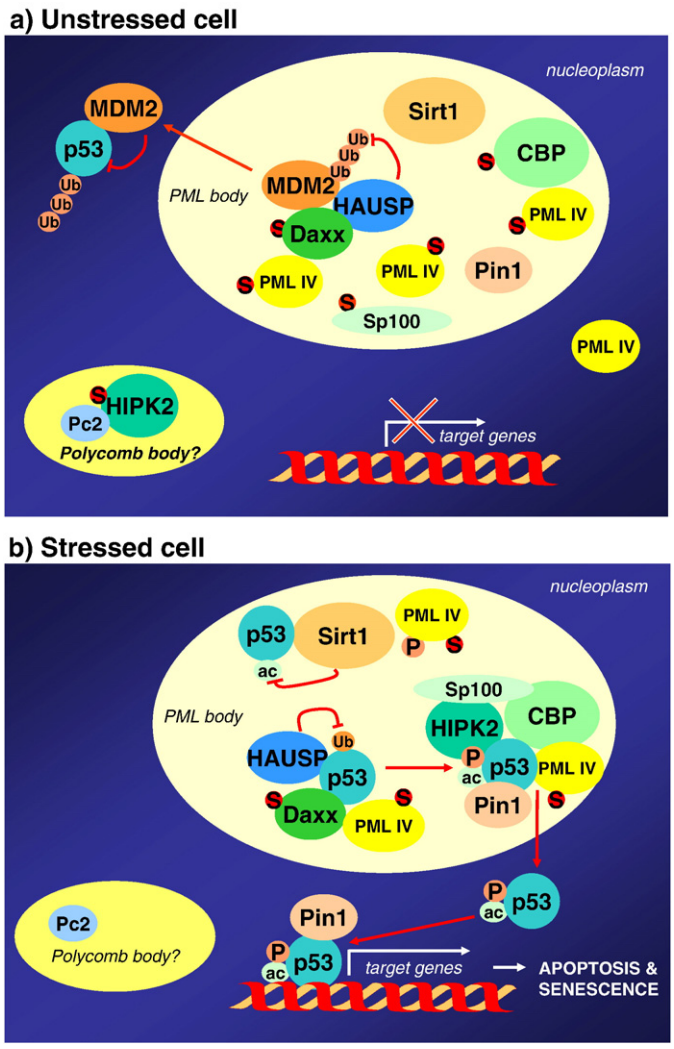

Fig. 2. Control of p53 activity at PML NBs. A hypothetical model is shown. (a) In unstressed cells, a complex of Daxx and the deubiquitinase HAUSP stabilizes the MDM2/HDM2, which polyubiquitinates p53 and leads to its proteasomal degradation. It is currently unclear whether this takes place at PML NBs. HIPK2 mainly resides in non-PML NBs in absence of genotoxic stress. (b) Upon cytotoxic stress, p53 is phosphorylated and the HAUSP-MDM2-complex dissociates leading to MDM2 degradation and p53 stabilization. p53 is recruited into PML NBs through interaction with PML-IV. These events uncouple p53 from MDM2-dependent negative regulation. In response to severe genotoxic stress, HIPK2 is recruited by PML-IV into PML NBs were it forms a complex with CBP and p53. HIPK2 phosphorylates p53 at Ser46 and thereby regulates p53 acetylation at Lys382. This may affect p53's interactions with cofactors and thus enhance its affinity to target genes that drive the cell into apoptosis or cellular senescence. This process is counteracted by the deacetylase SIRT1, which deacetylates the p53 Lys382. The prolyl-isomerase Pin1 induces conformational changes in p53 in response to p53 phosphorylation, potentiating p53 acetylation and dissociation from MDM2. It is currently unclear whether this occurs at PML NBs or the chromatin of the target promoters.

stability. DNA damage leads to the dissociation of this complex and hence to the degradation of MDM2, which in turn stabilizes p53 [75,76]. In parallel, HAUSP can directly stabilize p53 by deubiquitinating it, also contributing to p53-mediated apoptosis [77].

Thus, several competing apoptosis-regulating mechanisms converge at PML NBs (summarized in Fig. 2). Further research is required to elucidate the crosstalk between activation and inactivation of p53, as well as p53-dependent and -independent apoptosis regulation.

4. PML NBs and death-receptor signalling

PML NBs play also a role in apoptosis regulation via the extrinsic apoptotic pathway (Fig. 3). For instance, the FLASH protein, also termed CASP8AP2 (caspase-8 associated protein 2), which has been originally implicated in caspase-8 activation at the level of the CD95 DISC [78], partially colocalizes with the PML NB component Sp100 and with PML itself [41]. FLASH was also found in Cajal bodies, where it regulates histone gene expression and cell cycle progression [79,80]. Upon engagement of the death-receptor CD95/Fas in the type II cell line HT1080, FLASH leaves NBs and migrates into the cytoplasm, accumulates at mitochondria and interacts with and facilitates cleavage of caspase-8, thereby enhancing cell death. Knockdown of FLASH, in turn, renders the cells more resistant to extrinsic apoptosis induction [41]. Interestingly, FLASH/CASP8AP2 appears to be a prognostic marker in childhood acute lymphoblastic leukemia, where lower levels of FLASH correlate with decreased sensitivity of the leukemic cells to apoptosis induction and with less event-free survival of the patients [81].

In leukemic blasts, it was found some years ago that TRAIL can be upregulated by PML [82], but the factor that is targeted directly by PML had not been identified. Interestingly, in a very recent study it was shown that PML can enhance the activity of the transcription factor NFAT (nuclear factor of activated T-cells), which induces the transcription of the genes coding for FasL, TRAIL and TNFα, facilitating death-receptor-mediated apoptosis [83].

The PML NB component Daxx has also been linked to death-receptor-mediated apoptosis (recently reviewed in [84]). Daxx was originally reported to promote apoptotic cell death by interacting with the intracellular portion of CD95/Fas, either directly or via the death domain protein FADD (Fas-associated death domain). Obviously, Daxx also interacts with the pro-apoptotic kinase ASK1 (apoptosis signal-regulating kinase1) and induces the CD95-JNK signalling axis to engage the apoptosis machinery. In addition, Daxx is critical for JNK activation via the TGF-β pathway and in response to oxidative stress or UV irradiation. Moreover, Daxx can act as transcriptional repressor for several transcription factors, for instance for the p65/RelA subunit of the pro-survival factor NF-κB (nuclear factor-κB), thus preventing expression of anti-apoptotic genes. Thus, it was suggested that Daxx may indeed modulate CD95-dependent apoptosis induction from PML NBs rather than from the DISC. SUMO-1-conjugated Daxx can be recruited by PML into PML NBs [33], a process which also requires a SIM within Daxx [85]. NB-associated Daxx appears to be inactive with respect to apoptosis induction [86], so under steady-state conditions, PML would exert an anti-apoptotic function by blocking Daxx. Indeed, in rheumatoid arthritis fibroblasts, overexpression of SUMO-1 correlates with strong nuclear PML sumoylation, increased recruitment of Daxx into PML NBs and resistance of the cells to CD95-induced apoptosis [87]. Moreover, in PML NBs, Daxx partially colocalizes with and is earmarked for degradation by Pin1, which reduces death-receptor-mediated apoptosis via the Daxx-JNK (c-*jun* N-terminal kinase)-pathway [56]. Conversely, HIPK2 was shown to phosphorylate Daxx, which may release Daxx from PML NB [88]. Collectively, the effects of Daxx on different apoptosis pathways are pleiotropic, and the relationship between these effects still remains to be further investigated [84].

5. PML NBs and TGF-β receptor signalling

Less than 50% of the nuclear PML is actually sumoylated and associated with NBs (e.g. [89]). The remaining half of the protein is distributed throughout the nucleoplasm and was even shown to shuttle to the cytoplasmic compartment. Some potentially tumourigenic mutations may act by sequestering nuclear PML, but also the comparatively abundant normally occurring isoform PML-I probably contains a functional nuclear export signal (NES) and is found in both NBs and the cytoplasm [21]. Interestingly, there is evidence for a function of cytoplasmic PML (cPML) in the transduction of TGF-β (transforming growth factor-β) signals that cannot be fulfilled by nuclear PML. Lin et al. could show that *Pml−/−* fibroblasts are refractory to TGF-β-induced apoptosis, and sensitivity of these cells

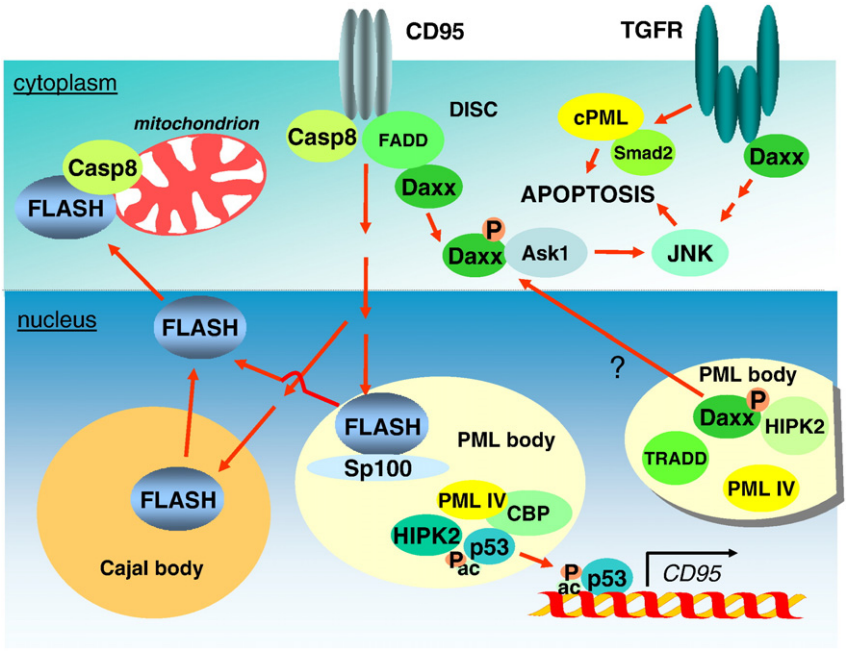

Fig. 3. Role of PML NBs in receptor-mediated apoptosis signalling. PML can influence the extrinsic apoptotic pathway at multiple sites. The FLASH protein, which is partially localized in PML NBs where it interacts with Sp100, is released from NBs and the nucleus upon CD95 activation and is targeted to mitochondria. At mitochondria, FLASH facilitates caspase-8 processing and apoptosis induction via the mitochondrial pathway. The Daxx protein can transmit the CD95 death signal through activating the JNK pathway due to interaction with FADD at the CD95 DISC, and it may also participate in TGF-β-mediated JNK activation. Daxx also resides in PML NBs, where it may regulate TGF-β-dependent apoptosis by repress pro-survival signalling (not shown). Daxx may be released from PML NB after HIPK2-mediated phosphorylation. Moreover, p53 phosphorylated at Ser46 and acetylated at Lys382 can activate genes coding for components of death-receptor pathways, such as CD95 receptor and its ligand, thus coupling the intrinsic and the extrinsic death pathway.

towards TGF-β signalling could only be re-established by expression of cPML, which is a predominantly cytoplasmic isoform that lacks the sequence encoded by exons 4 to 6 [90]. Mechanistically, they showed an interaction of cPML with both Smad2 (SMA and mothers against decapentaplegic 2) and SARA (Smad anchor for receptor activation), leading to a recruitment of these proteins to the early endosome compartment. Another study presented evidence for an inhibitory mechanism where TGIF (TG-interacting factor) forms a ternary complex with c-*jun* and PML, sequestering cytoplasmic PML in the nucleus and blocking its function in TGF-β signalling [91].

The multifunctional Daxx protein has also been implicated in TGF-β signalling [92]. In this context, Daxx was found to interact with the cytoplasmic domain of the type II TGF-β receptor and to be critical for activation of the JNK pathway. How could PML NB-associated Daxx be released from and targeted to the cytoplasm where it is supposed to act in TGF-β signalling? A possible mediator

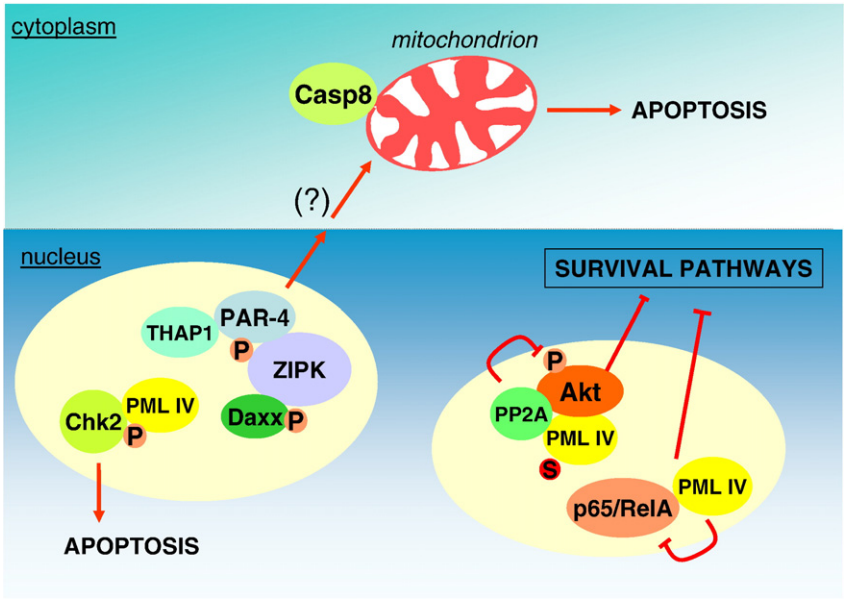

Fig. 4. Role of PML NBs in p53- and death-receptor-independent apoptosis, and the control of survival signalling. PML can induce apoptosis in a Daxx- and death-receptor-independent manner when phosphorylated by Chk2 on Ser117 upon IR. Moreover, complexes of the pro-apoptotic protein PAR-4, the Dlk/ZIPK protein kinase, Daxx and presumably the THAP protein can also trigger apoptosis, which may occur mainly via the mitochondrial pathway. In addition, pro-survival signalling pathways are negatively regulated by PML, as it can recruit active, phosphorylated-Akt kinase into NBs, where it is dephosphorylated by the phosphatase PP2A. Furthermore, PML can sequester the transactivating NF-κB subunit p65 into NBs and thereby prevent its binding to anti-apoptotic targets gene promoters.

of this re-targeting might be HIPK2, which was shown to phosphorylate Daxx and to release Daxx from PML NBs when exogenously expressed [88]. HIPK2 also appears to cooperate with Daxx in TGF-β-dependent activation of JNK, which also leads to apoptosis in a p53-independent manner [88]. This aspect of HIPK2 function was shown to be blocked by sumoylation of HIPK2, which did not interfere with p53 phosphorylation at Ser46 [88]. However, it is currently unclear whether HIPK2 controls Daxx localization under physiological conditions.

6. PML NBs and other apoptosis pathways

A novel pathway that leads to PML-facilitated apoptosis independently of p53 may involve the action of a complex of the death-activated protein-like kinase DLK/ZIPK, Daxx [93], the nuclear pro-apoptotic protein THAP1 and the prostate apoptosis-response factor PAR-4 which antagonizes NF-κB [94]. These factors seem to interact at PML NBs [95], but the mechanism by which this promotes apoptosis remains to be clarified, although it seems to involve the mitochondrial pathway [96]. PML may also induce apoptosis in another p53-independent manner that depends on its phosphorylation on Ser117, which is mediated by Chk2 in response to ionizing-irradiation [97]. This work by Yang et al. revealed that a phosphorylation-mimetic PML Ser117Glu mutant could induce apoptosis in p53-deficient cells, whereas Ser117Ala failed to do so. However, the pathway that is affected by Ser117 phosphorylation affects neither death-receptor-mediated apoptosis nor abundance and localization of Daxx and therefore still remains to be identified. The current knowledge about the alternative pathways by which PML can regulate apoptosis is depicted in Fig. 4.

7. PML NBs and cell survival signalling

PML NBs can also regulate survival signalling. For instance, the sensitivity of U2OS cells towards TNFα-induced apoptosis is enhanced by the ability of PML to interact with and thereby block the transcriptional activity of the NF-κB subunit RelA/p65 [32]. Furthermore, a recent study by Trotman et al. showed that PML mediates the recruitment of phosphorylated Akt into NBs, where the phosphorylation mark is removed by the phosphatase PP2A [98]. This inhibits its ability to phosphorylate FOXO (Forkhead box) transcription factors, which increases their ability to activate pro-apoptotic target genes such as *Bim* and *TRAIL*. Moreover, another study suggests that PML-IV can repress the expression of the anti-apoptotic protein survivin on the transcriptional level [99], thereby removing survivin from caspase-9 and facilitating apoptosome formation. It was shown that PML represses the *Survivin* promoter independently of p53, but a direct binding of PML to this region has not been demonstrated; therefore, the PML effect may also occur via an intermediate factor associated with PML NBs. Thus, PML not only actively promotes apoptosis, but also interferes with survival signalling pathways (Fig. 4).

8. Crosstalk of PML NBs with other NBs in apoptosis regulation

Several lines of evidence indicate crosstalk between PML NBs and other nuclear domains (summarized in Fig. 5). PML NBs, similar to other nuclear domains such as Cajal bodies or nucleoli, are dynamic structures that constantly exchange their components with the surrounding nucleoplasm and other NBs [10,100,101]. Some proteins such as HIPK2, Sp100, FLASH or HDM2 have been found in other nuclear domains, such as Cajal bodies (FLASH) [79,80] or the nucleolus (HDM2) [102], or in as yet not fully characterized domains (HIPK2) [38]. Moreover, PML NBs are often found in close proximity to Cajal bodies (e.g. [80]), which may be due to an interaction between the PML NB-associated protein PIASy and the constitutive Cajal body component coilin [103]. Cajal bodies also seem to fragment into smaller bodies upon UV irradiation, quite similarly to PML NBs [104]. Cajal bodies, in turn, share several proteins such as fibrillarin with nucleoli, and are often associated with nucleoli [105], which suggest functional interplay and crosstalk with these domains.

Remarkably, nucleoli, which are established sensors for cell stress, are the nuclear domains that share the most proteins with PML NBs,

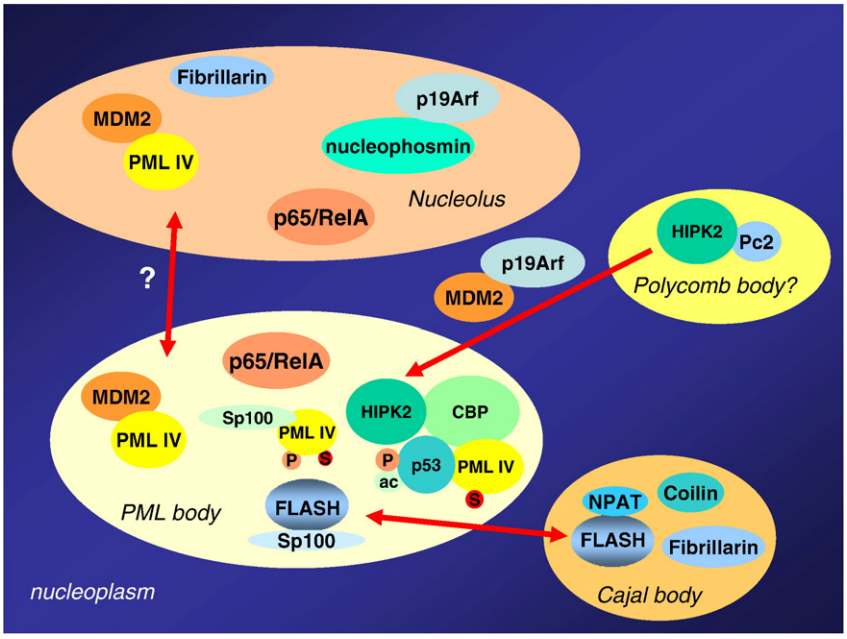

Fig. 5. Crosstalk between different nuclear bodies in apoptosis regulation. PML NBs and other subnuclear structures share various components and contribute to cell fate decisions. For instance, the nucleolus shares fibrillarin and NUPP140 with Cajal bodies. FLASH not exclusively resides in PML NBs, but also in Cajal bodies, which are often found juxtaposed to PML NBs. HIPK2 NBs in unstressed cells may, in part, correspond to polycomb bodies. In response to DNA damage, HIPK2 is then partially recruited to PML NBs. PML was shown to sequester the p53 ubiquitin ligase MDM2/HDM2 to the nucleolus, which plays a critical role as a stress sensor. The nucleolus can directly regulate p53-dependent apoptosis by releasing p19Arf in response to cytotoxic stress, which then leads to the inhibition of MDM2 function. Also, the NF-κB subunit p65 can be sequestered in the nucleolus, thus inhibiting the activation of anti-apoptotic target genes.

and are also known to recruit and release a variety of proteins upon cellular stress [106]. Indeed, it was shown that certain PML isoforms, namely PML-I and PML-IV, can even form "nucleolar caps" upon cellular stress [107], and that PML is able to sequester MDM2 to the nucleolus in a manner dependent on ATR [102], thereby stabilizing p53. Moreover, a recent study [108] suggests that the RelA subunit of the pro-survival factor NF-κB can also be sequestered in the nucleus after cytotoxic stress, which also increases apoptosis in affected cells, although in this case, in contrast to the study by Wu et al. [32], PML involvement has not been demonstrated. The nucleolar sequestration of p65/RelA can also be induced by Cdk4 (cyclin-dependent kinase 4) inhibition, either by p38 or by CDK4 inhibitors [109,110]. Moreover, the tumour suppressor p19ARF (alternate reading frame) is localized in the nucleolus in unstressed cells, in a complex with the phosphoprotein nucleophosmin [111], and is released upon cytotoxic stress [112], engaging the p53-dependent apoptotic pathway by binding to MDM2. Interestingly, ARF mediates the sumoylation of MDM2 [113], which it was also reported to sequester in the nucleolus [114]. Very recent work suggests that localization of ARF in the nucleolus is indeed mediated by nucleophosmin, but is not required for the p53-activating function of ARF [115], supporting the hypothesis that nucleolar sequestration of ARF rather promotes cell survival. The nucleolus may modulate apoptosis in PML- and p53-independent ways, for instance bystress-dependent release of nucleophosmin, which then acts as a Bax chaperone that recruits Bax to mitochondria to facilitate apoptosis [116], or by facilitating recruitment and degradation of the recently identified survivin splice form survivin-deltaEx3, which paradoxically seems to be required for its anti-apoptotic function [117].

In summary, the nucleolus – beside PML NBs – is emerging as a second subnuclear compartment with complex functions in apoptosis regulation, exhibiting extensive crosstalk with PML NBs. Other nuclear structures, such as the HIPK2 NBs, Cajal bodies and FLASH- and Sp100-containing bodies, were also shown to exchange protein with PML NBs, but a direct role of these compartments in apoptosis induction has not been demonstrated yet.

9. PML and cancer

Apoptosis and cellular senescence are crucial mechanisms to prevent cellular transformation and malignant cell growth of damaged cells. Consistently, PML activity has been linked to tumour suppression. In many cancer types, PML protein is reduced or almost completely lost by post-transcriptional mechanisms [118,119], and that loss is associated with tumour progression in prostate and breast cancer. Most recently, it has also been shown that PML can repress carcinogenesis by repressing the hypoxia-induced factor HIF1α (and thereby tumour angiogenesis) by inhibiting mTOR [120]. Furthermore, some human tumour virus-encoded proteins such as human Papilloma virus (HPV) 18 E6 protein and the Hepatitis C virus (HCV) core protein may contribute to the development of cervix or hepatocellular carcinoma, respectively, by targeting PML functions at PML NBs [121,122].

However, the classical example for the function of PML as a suppressor of malignant cell growth is acute promyelocytic leukemia (APL) (for a recent review, see [123]). The promyelocytes of more than 90% of patients that suffer from this disease express of a protein chimera of PML fused to the retinoic receptor alpha (PML-RARα) that is produced as a result of a reciprocal translocation between chromosomes 15 and 17 [123]. The PML-RARα oncoprotein always contains the RBCC domain of PML and can still interact with the remaining wildtype PML in APL cells. However, PML-RARα does not localize to NBs, but instead delocalizes PML into a microspeckled pattern, blocking the activity of the wildtype PML expressed from the intact allele in a dominant-negative manner [124,125]. Furthermore, Gurrieri et al. identified mutations of the *PML* gene in two cases of APL which were particularly aggressive [119], indicating that loss of PML function really is an important player in the pathogenicity of APL.

The APL cells have been shown to be resistant to some apoptotic stimuli. For instance, TNFα-, but not CD95-mediated apoptosis is strongly reduced in APL cells [126]. Moreover, overexpression of PML-RARα in myeloid precursor cells was shown to inhibit their differentiation and to prevent starvation-induced apoptosis [127]. Treatment of APL cells with retinoic acid (RA) has been shown to revert the dominant-negative phenotype of PML-RARα by degrading the chimeric protein, through caspase-mediated cleavage of PML-RARα [128] or via the proteasomal pathway [129], re-establishing functional PML NBs, although not directly inducing apoptosis, but rather differentiation of the APL cells. In contrast, arsenic trioxide (ATO), another potent therapeutic that is used to treat myeloid leukemias, induces programmed cell death in APL cells [130]. ATO can induce phosphorylation of PML by ERK2 (extracellular signal-regulated kinase 2) in non-APL cells; interestingly, PML-RARα is also phosphorylated by ERK2, but this does not result in SUMO modification of the hybrid protein [130]. However, ATO activates ATR kinase, which then phosphorylates Chk2-T68 in a Chk1- and ATR-independent manner. This results in PML-dependent autophosphorylation of Chk2 which in turn triggers the p53-dependent apoptotic pathway [131]. Moreover, ATO induces the degradation of PML-RARα, thus enabling the wild type PML to relocalize to NBs, in which Chk2 is autophosphorylated and fully activated, constituting a positive feedback loop enhancing apoptosis in the treated cells [132]. ATO also reduces the levels of the anti-apoptotic protein Bcl-2 at the mRNA level [133] and upregulates the death-receptor ligand TRAIL, which was shown to induce apoptosis in APL cells in a paracrine manner [134]. Remarkably, ATO not only leads to the degradation of RML-RARα, but also that of wild type PML [135], which requires sumoylation of PML at lysine 160 [136]. Two independent studies now show that this degradation is mediated by RNF4/SNURF, the first known SUMO-chain specific E3 ubiquitin ligase [137,138]. This suggests that PML NBs may be degradation centres for PML and other PML-associated proteins such as Daxx, which are recruited to PML NBs via SUMO binding. To date, it is entirely unclear under which circumstances this mechanism has an impact on apoptosis regulation by PML, since ATO-treated cells die by p53 dependent- and independent apoptotic pathways, but RNF4-dependent degradation also seems to occur under steady-state conditions [137], thus likely preventing apoptosis and cellular senescence in unstressed cells by keeping PML levels below a "dangerous" threshold.

10. Conclusions

It is now well established that PML NBs integrate cytotoxic stress signals and are critical mediators of p53 dependent and -independent apoptosis. Although some of the mechanisms by which NB-associated PML can enhance apoptosis appear to be fairly well analysed, such as the facilitation of the phosphorylation and acetylation of p53 upon DNA damage induction, many questions await further investigation. For instance, the relationship between different PML splice forms and their potential differential regulation is far from clear. Along the same lines, it has been shown that these splice forms do not localize to NBs to the same extent, and kinetic analyses show that many PML isoforms are exchanged within minutes between a given nuclear body and the surrounding nucleoplasm, and can also be recruited to specific target promoters or even to cytoplasmic structures, so that it will be a tough task to really separate body-associated from nucleo- or cytoplasmic functions of PML protein(s). The analysis of specific PML isoforms may also reveal novel interactions that may point to other regulatory functions of PML NBs. Also, the often observed juxtaposition of PML- and other NBs may be a hint that PML may influence or monitor more intranuclear processes as previously anticipated by talking to other NBs and vice versa. Moreover, some known interactions of PML with

proteins such as ZIPK, PAR-4 or Chk2 trigger apoptosis, but the underlying mechanisms are unclear and require further investigation.

Finally, it will be highly interesting to clarify whether the RING-domain protein PML itself influences cell fate decisions by acting as either a ubiquitin ligase or a SUMO ligase, which was suggested by experiments in yeast [18]. In addition, it remains to be studied whether PML can recruit other sumoylated proteins to be regulated by RNF4 or mechanistically-related ligases. This will allow important insight into the mechanisms by which PML regulates the activity of its interaction partners. Answers to these questions will help to draw a more detailed picture about the role of PML NBs in cell fate regulation and tumour suppression. This may allow us to forge novel molecular weapons for the fight against cancer.

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